REMARKS

Claims 1-9, 11, 12, 18, 20, 22, 24 and 28-40 are now in the case.

Reconsideration of this Application and entry of the foregoing amendments are requested. The claims have been amended in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. Claims 10, 13, 14-17, 19, 21, 23, 25 and 26-27 have been cancelled without prejudice or disclaimer. Applicants reserve the right to reintroduce the subject-matter thereof in the future during the prosecution of the present application or an application derived therefrom. Additional support for claim 2 can be found for example at page 25, line 17. Additional support for the amendments to claim 4 can be found, for example, in Figure 2A, which shows as "S" the structure of oleantrose. The utility of pharmaceutical compositions of claim 11 was deleted. Claim 12 unites the different uses for the compositions of claim 11, as recited in old claims 11, 14 and 16. Support for new claim 28 can be found in Figure 2, for example. Further support for claim 30 can be found in Figure 2, as the claim now recites more particularly the chemical structure of the claimed compound. Further support for new claim 31 can be found in old claim 8. New claim 32 is identical to amended claim 11, except for its dependency. New claims 33-35 are identical to amended claims 18, 20 and 24, except for their dependencies. Similarly, new claims 37-39 are identical to amended claims 18, 20 and 22, except for their dependencies. New claim 40 is identical to new claim 33, except that the compounds are defined and supported by Figure 1.

REJECTION UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The Examiner has rejected claims 1-27 under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit that in view of the deletion of claim 10, as well as the terminologies "derivatives thereof" and "derivative" in claims 2, 7 and 8, the rejection for lack of enablement associated with the use of these terminologies has been rendered moot.

The Examiner concedes that "the specification provides evidence that MV8608 and MV8612 possess R-type Ca^{2+} channel blocking properties". However, the Examiner alleges that the specification "does not provide evidence that the claimed compositions and methods are effective in preventing various diseases or in

decreasing proliferation of cancer and tumor cells". The Applicants respectfully disagree with the Examiner since, as taught in Example 18, at page 63, MV8612 and MV8608 affect human lymphocyte proliferation *in vivo*. The Examiner is referred to Figure 53 and to page 63, between lines 6 and lines 10, where it is taught that MV8608 "caused great inhibition of human lymphocyte proliferation, with MV8612 being about 570 fold more potent". It is therefore respectfully submitted that, clearly, the compounds of the present invention are indeed taught to be potent inhibitors in proliferation of cells.

In addition, the Examiner is referred to Example 16, "*in vivo* results with compounds MV8608 and MV8612" which relate to experiments in mice and assess the anti-inflammatory activities of the compounds of the present invention. Example 17 is another animal model tested. Example 19 refers to the antinociceptive (anti-pain) actions of the compounds of the present invention. Applicants respectfully submit that in view of the number of experiments and results taught in the present invention and the disclosed diseases or conditions in which inflammatory responses occur, that a person of ordinary skill in the art would view the present invention as enabling for the treatment of the claimed diseases and conditions.

In view of the above and foregoing, it is respectfully requested that the Examiner withdraws his rejection of claims 1-27 under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-27 have also been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Applicants respectfully traverse the rejection as follows.

Rejection of claim 1 for using a preamble which reads on two structures while only showing one, has been overcome by the present amendment of the preamble.

The rejection of claim 1 for an alleged lack of clarity for the use of the terminologies "saponin-like derivatives thereof" (claim 1), "derivative of said saponin-like compound" (claim 2) and "derivatives thereof" (claims 7-8) has been rendered moot by the deletion of these terminologies.

Claim 1 has also been corrected, as suggested by the Examiner, to refer to "or a pharmaceutically acceptable salt thereof".

As suggested by the Examiner, the term "general" in claims 1-2 and 8-9 has been deleted.

Rejections of claims 8 and 9 are believed to have been overcome by the amendment to claim 8, and the amendment to claim 9 which is now dependent on claim 29 which uses the word "or".

The Examiner has rejected claims 11, 20 and 22 for the use of the term "preventing", as the Examiner alleges that "it is not clear whether prevention was achieved for a period of days, months, years or whether permanent prevention was achieved". This terminology has been deleted from claim 11. It is respectfully submitted that the terms "preventing" in claims 20 and 22 are clear and definite since a person of ordinary skill in the art would understand that the prevention of the disease or condition is associated with an administration of an effective amount of a compound of the present invention.

As indirectly suggested by the Examiner, claims 13, 14, 15, 16 and 17 have been deleted.

With respect to the objections of claims 5-7 and 10-27 under 37 CFR 1.75 "as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim", the Applicants respectfully submit that in view of the preliminary amendment filed March 28, 2000, which replaced all multiple dependent claims by mono-dependent claims, this objection has been rendered moot.

In view of the above and foregoing, it is respectfully requested that the Examiner withdraws his rejection of claims 1-27 under 35 U.S.C. § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 102(b) or 103(a)

Claims 1-27 have been rejected "under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Calixto et al. 1998 or Neves et al. 1993, Applicants respectfully traverse the Examiner's rejection as follows.

Applicants advise that the subject-matter of the various claims was commonly owned at the time the invention covered therein were made.

Neither the structure nor the biological activity of the claimed compounds were known or suggested in the art, prior to the filing of the priority

application on which the instant application is based. The claimed compounds and their use as specific steady-state R-type Ca^{2+} channel blocker were not known or suggested prior to the present invention.

The paper of Calixto et al., in the Br. J. Pharmacol. 1988 only teaches the presence of a crude compound fraction called MV8612. The isolation and structure of the active compound and MV8612 were not disclosed prior to the present invention. Calixto et al. merely teach:

> "These anti-Bk compounds which appear, from preliminary spectral analysis, to be terpene glycosides". (at page 1134, right column, line 1)

and the fact that the compounds are "non-peptide compounds", for example see page 1133, line 1. Moreover, Calixto et al. teach at page 1134, right column, last sentence of the first full paragraph

> "More details on the isolation procedures and the physical and chemical characterization of these compounds will be published elsewhere."

These results were never published.

Similarly, only a brief description of the method of isolation and identification of the crude compound called MV8612 were described in the paper of Neves et al. (Eur. J. Pharmacol. 243: 213-219, 1993). Neves et al. merely describe that the crude compound called MV8612 is a steroidal glycoside ($C_{60}H_{94}O_{23}$) MW1182 (1214, left column, section 2.1). Of note, Neves et al. teach at the next sentence "details of the isolation and chemical characterization of compound MV8612 will be published elsewhere". Again, such results were never published.

The Applicants respectfully submit that the information given in Calixo or Neves together or separately on the structure of MV8612: "non-peptide" compound, "terpene glycosides" or "steroidal glycoside" is far from sufficient, even to a person having <u>outstanding</u> skill in the art at the time the instant invention was made, to imagine the structure of the claimed compounds and more particularly the structure as claimed in claims 1, 2 and 28. In addition, from a biological activity point of view, Calixto and/or Neves do not teach or even suggest that the compounds obtained from fractions of Mandevilla Velutina (undefined by Calixto and Neves) are steady-state R-type Ca^{2+} channel blockers. For example, the published papers of

two of the inventors, Drs Calixto and Yunes based on the use of crude fractions containing the claimed compound of the present invention were taught as bradykinin receptor blockers. This was later shown to be erroneous (Bkaily et al., 1997, Can. J. Physiol. Pharmacol. 75: 652-666).

In any event, it is respectfully submitted that Calixto or Neves, together or separately, neither teach nor suggest the claimed structure of the compounds of the present invention or their biological activity as R-type Ca^{2+} channel blockers.

CONCLUSIONS

The rejections of claims 1-27 are believed to have been overcome by the present remarks and by the amendments to the claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such an action is earnestly solicited.

In the event that there are any questions concerning the amendment or application in general, the Examiner is respectfully urged to telephone the undersigned so that the prosecution of the application may be expedited.

Authorization is hereby given to charge deposit account no. 13-2725 for any deficiencies or overages in connection with this response.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
(612) 332-5300

Gregory A. Sebald
Reg. No. 33,280

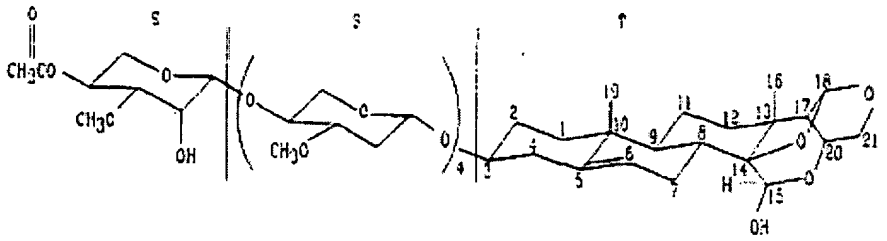
Dated: September 28, 2001
Encls.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1-9 and 11-12 have been amended as follows: Underlines indicate insertions and brackets "[ ]" indicate deletions.

1. (Amended) A compound having the [general formula of MV8612 analogs VIIA and VIIB] formula:



[saponin-like derivatives thereof and] or a pharmaceutically acceptable salt[s] thereof.

2. (Amended) A [saponin-like] compound having the [general] formula EST [or a derivative of said sanopin-like compound], wherein:

a) E and S define a saponin oligosugar portion, with E defining the terminal sugar portion thereof[,];

b) and T defines a steroid-like portion[;], wherein T is a pregnane-3β-ol derivative.

3. (Amended) The compound of claim 2, wherein S is selected from the group [comprising] consisting of a tetra sugar derivative, a monomeric sugar derivative and an aligomeric of sugar derivatives.

4. (Amended) The compound of claim 2, wherein S is selected from the group consisting of α(1-4) (2-deoxy, 3-methoxy),-L-lyxotetrose, α(1-4) (2-deoxy, 3-methoxy) L-xylotetrose, α(1-4) (2-deoxy, 3-methoxy)-L-arabinotetrose, α(1-4) (2-deoxy, 3-methoxy)-L-xylotetrose, α(1-4) (2-deoxy, 3-methoxy-L-ribopyranotetrose, α(1-4) (2-deoxy, 3 methoxy-L-sorbotetrose,

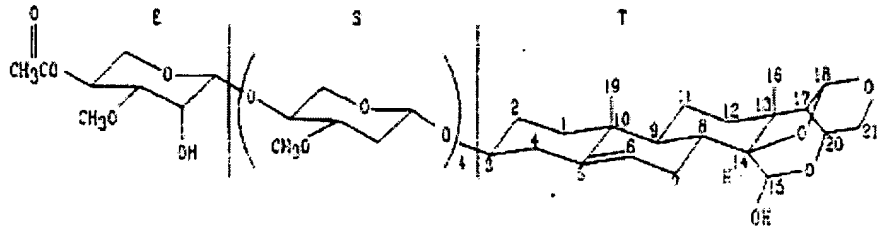
α(1-4)-L-lyxotetrose, α(1-4)-L-xylotetrose, α(1-4)-L-arabinotetrose, α(1-4)-L-xylotetrose, α(1-4)-3, 4 methoxy-L-lyxotetrose, α(1-4)-3, 4 methoxy-L-xylotetrose, α(1-4)-3,4 methoxy-L-arabinotetrose, α(1-4)-3,4 methoxy-L-xylotetrose, α(1-4)-3,4 methoxy-L-ribopyranotetrose, α(1-4)-3,4 methoxy-L-sorbopyranotetrose, α(1-4)-L-lyxotetrose, α(1-4)-L-xylotetrose, α(1-4)-L-arabinotetrose, α(1-4)-L-ribopyranotetrose, oleantrose, and α(1-4)-L-sorbotetrose.

5. (Amended) The [saponin-like] compound of claim 2, wherein E is selected from the group consisting of 4-acetoxy-3 methoxy-L-α-lyxose, 4-acetoxy-3-methoxy-L-α-xylose, 4-acetoxy-3-methoxy-L-α-arabinose, 4-acetoxy-3-methoxy-L-α-xylose, -acetoxy-3-methoxy-L-α-ribopyranose, diacetylfucose, and 4-acetoxy-3-methoxy-L-α-sorbose-acetoxy.

6. (Amended) The [saponin-like] compound of claim 2, wherein T is selected from the group consisting of 5-pregnane-3-ol oxytricyclo- 15-ol, illustrol, 5-pregnane-3-ol-20-one, cholesterol, cholic acid, ergosterol, stigmasterol, androstenon, digitoxygenin, β-sitosterol, uvaol, ursolic acid, sarsasapogenin, 18,β -glycyrrhetinic acid, betulin, betulinic acid, oleanoic acid, and padocarpic acid.

7. (Amended) The [saponin-like] compound of claim 2, wherein said compound [and derivatives thereof are[is capable of displaying an inhibitory activity of the steady state R-type calcium channel.

8. (Amended) A R-type Ca^{2+} channel blocker having the [general] formula[of compound VIIA and compound VIIB]:



[and derivatives thereof] or a pharmaceutically acceptable salt thereof.

9. (Amended) A specific R-type calcium channel inhibitor having the [general formula **I (IA and IB), II, III, IV, V, VI, VIIA and VIIB** as set forth in Fig. 1 and Fig. 2] the structure of the compound of claim 29.

11. (Amended) A pharmaceutical composition [for treating or preventing or blocking overstimulation of R-type Ca^{2+} channels associated with a disease or condition in a warm blooded animal,] comprising at least one compound of claim 1, together with a pharmaceutically acceptable carrier.

12. (Amended) The pharmaceutical composition of claim 11, for at least one of treating or blocking overstimulation of R-type Ca^{2+} channels associated with a disease or condition in a warm blooded animal, or for blocking or relieving side effects of a drug which overstimulate R-type CA^{2+} channels, or for the prevention or treatment of a disease or condition in which a sustained elevation of $[Ca]_c$, $[Ca]_n$ or R-type Ca^{2+} blocking is encountered[, wherein said compound does not significantly affect the basal activity of said R-type Ca^{2+} channel].